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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/349,489	12/02/1994	DAVID B. RING	0999.001	6479

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EXAMINER
HUNT, JENNIFER ELIZABETH

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/349,489	Applicant(s) RING
	Examiner Jennifer Hunt	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 18, 2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-4 and 8-15* is/are pending in the application.

4a) Of the above, claim(s) *4 and 9-14* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 8, and 15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Continued Prosecution Application

1. The request filed on 12-18-2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/349,489 is acceptable and a CPA has been established. An action on the CPA follows.

2. Acknowledgment is made of applicant's cancellation of claims 5-7. Claims 4 and 9-14 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1-3, 8, and 15 are under consideration.

Claim Rejection Maintained

3. The grounds of rejection of pending claims 1-3, 8, and 15 under 35 U.S.C. 103(a) as being unpatentable over Hsieh-Ma et al. (Cancer Research, 1992), Weiner et al., (Cancer Research 1993), or Ring et al., (Breast Epithelial Antigens, 1991), in view of Fanger et al. (Critical Reviews in Immunology, 1992) or Snider et al., (J. Exp. Med. 171:1957-1963, 1990) is maintained for reasons set forth below.

As set forth in the previous Office Actions, and summarized herein for clarity, Hsieh-Ma et al., Weiner et al., or Ring et al., teach induction of an immune response in a patient, a xenograft mouse, which meets the limitation of the definition of patient as specified at page 8 of the instant disclosure. Although the references fail to teach an induction of antibody production to the second antigen (c-erb-B2), Fanger et al. and Snider et al. teach the known method

comprising administering bispecific antibodies, (and optionally antigen) to induce or enhance the production of antibodies targeted to the second antigen, and further that bispecific antibodies targeted to APC cell antigens (including FcgRIII) induce production of antibodies to the second antigen.

Applicant argues that the amendments to the claims overcome the rejections. Specifically, applicant argues that the incorporation of the limitations of dependent claims 6 and 7 into claim 1 further characterizes the second antigen, and that the removal of 520C9 as a possible second binding site causes the art of record which teaches the 2B1 antibody to non-longer apply. Applicant's arguments filed 8-30-2001 have been fully considered but they are not persuasive.

The instant claims recite that the second binding site can be 741F8. Weiner et al. teaches that the 741F8 antibody binds to the same epitope as the parent of 2B1, 520C9 (see page 99, first column). Thus the 2B1 antibody still meets the limitation that the second binding site binds the c-erbB-2 antigen and further comprises a binding site derived from a monoclonal antibody produced by the hybridoma 741F8 (HB 8490). The specification defines a "binding site derived from a monoclonal antibody" as a binding site in a second antibody having the same or homologous CDRs as the antibody, where homologous CDRs include one set of CDRs from an antibody in which the primary sequence of each CDR is at least 50% identical to the antibody and the binding site formed by these CDRs binds the same epitope as the monoclonal. While the instant references does not explicitly recite that the CDR's of 741F8 are at least 50% similar to the 520C9 arm of 2B1, absent evidence to the contrary, it appears that they would exhibit

significant homology because the parent antibodies (741F8 and 520C9) cross react and bind the same epitope. Further, it is noted that the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibodies with the 2B1 antibody of Hsieh-Ma et al., Weiner et al., or Ring et al., the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibodies with the antibody and the 2B1 antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

With regard to claim 8, it is further noted that hybridoma CRL 10197 produces the 2B1 antibody, which is explicitly taught in the prior art references.

4. The grounds of rejection of claim 6 under 112 first paragraph for lacking written description for failing to meet deposit requirements is applied to newly amended claim 1.

Applicant argues that the deposit requirements have been met, pointing to page 30 of the specification and a newly submitted declaration, however some required elements of the statement regarding deposit are missing:

With regard to the deposit text in the specification, the text does not state the date of deposit, or that all restrictions on the availability to the public of the material will be irrevocably removed upon the granting of a patent.

Further, there is no deposit for Ab 36H3 (11768).

New Grounds of Rejection

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3, 8, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "an antigen recognized by any of the following hybridomas". Hybridomas would not be capable of recognizing an antigen. Amending the claims to recite "an antigen recognized by a monoclonal antibody produced by any of the following hybridomas" would obviate this grounds of rejection.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 5, 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the bispecific antibody 2B1 and methods of inducing an immune response by administering the antibody, does not reasonably provide enablement for methods of inducing an immune response using any bispecific antibody which binds FcgRIII and

c-erbB-2 where the arm that binds c-erbB2 is "derived from" any of the numerous monoclonal antibodies recited in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn to a method of inducing an immune response using any bispecific antibody which binds FcgRIII and c-erbB-2 where the arm that binds c-erbB2 is "derived from" any of the numerous monoclonal antibodies recited in claim 1. The specification defines a "binding site derived from a monoclonal antibody" as a binding site in a second antibody having the same or homologous CDRs as the antibody, where homologous CDRs include one set of CDRs from an antibody in which the primary sequence of each CDR is at least 50% identical to the antibody and the binding site formed by these CDRs binds the same epitope as the monoclonal. Thus the claim encompass numerous variants in the CDR regions. Further, is not clear which CDRs can be modified and still meet the limitation set forth in the claims and defined in the specification.

The specification discloses only a trail in which 11 patients with c-erbB-2 overexpressing cancers are administered 2B1, a bispecific antibody known in the art. The specification also includes two examples of induction of an immune response in vitro, using 2B1. The specification does not make or use any other bispecific antibody except for the art known 2B1 antibody. Further, no antibodies "derived from" 2B1 are used, in that no changes in the CDRs of 2B1 are effected, and thus it is not clear that any antibody except for the 2B1 antibody known in the art would function in the instantly claimed methods.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single

amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody in unspecified order and fused to any human or nonhuman framework sequence, provided only that they exhibit 50% homology to the recited antibodies of claim 1, would have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

As evidenced by Adair et al. (PCT GB90/02017) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (p. 4). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

9. Claims 1-3, 8, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hsieh-Ma et al. (Cancer Research, 1992), Weiner et al., (Cancer Research 1993), or Ring et al., (Breast Epithelial Antigens, 1991), in view of Fanger et al. (Critical Reviews in Immunology, 1992) or Snider et al., (J. Exp. Med. 171:1957-1963, 1990), and further in view of Ring, US Patent 6,054,561.

Hsieh-Ma et al., Weiner et al., or Ring et al., and Fanger et al. or Snider et al. teach as applied to claims 1-3, 8, and 15 supra. Hsieh-Ma et al., Weiner et al., or Ring et al., and Fanger et al. or Snider et al. fail to specifically recite a second binding arm derived from 452F2, 741F8, or 454C11.

Ring, US Patent 6,054,561 teaches the anti-c-erbB-2 antibodies 452F2, 741F8, and 454C11, and that they all bind to the same epitope as 520C9 (see column 27, lines 1-26.)

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to substitute the any of the 452F2, 741F8, and 454C11 c-erbB-2 antibodies of Ring, US Patent 6,054,561 for the 520C9 antibody in the 2B1 bispecific antibody and to use the resulting bispecific antibody to induce an immune response in a patient, and one would have been motivated to do so because both the c-erbB-2 antibodies of Ring, US Patent 6,054,561 bind the same epitope of c-erbB-2 as the 520C9 parent antibody of the bispecific antibody 2B1 which is established in the art to be effective in inducing an immune response. Further, "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form the third composition that is to be

used for the very same purpose: idea of combining them flows logically from their having been taught individually in the prior art." In re Kerkhoven (205 USPQ 1069, CCPA 1980).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

February 28, 2002

SHEELA HUFF
PRIMARY EXAMINER